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Generational Difference of Refractive Error and Risk Factors in the Handan Offspring Myopia Study

Zhong Lin,^{1,2} Tie Ying Gao,³ Balamurali Vasudevan,⁴ Vishal Jhanji,⁵ Kenneth J. Ciuffreda,⁶ Peng Zhang,³ Lei Li,³ Guang Yun Mao,^{1,7,8} Ning Li Wang,² and Yuan Bo Liang^{1,2}

¹The Affiliated Eye Hospital, School of Optometry and Ophthalmology, Wenzhou Medical University, Wenzhou, Zhejiang, China

²Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Ophthalmology and Visual Science Key Lab, Beijing, China

³Handan Eye Hospital, Handan, Hebei, China

⁴College of Optometry, Midwestern University, Glendale, Arizona, United States

⁵Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong, China

⁶Department of Biological and Vision Sciences, State University of New York College of Optometry, New York, New York, United States

⁷School of Environmental Science and Public Health, Wenzhou Medical University, Wenzhou, Zhejiang, China

⁸Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States

Correspondence: Yuan Bo Liang, The Affiliated Eye Hospital, School of Optometry and Ophthalmology, Wenzhou Medical University, No. 270 West College Road, Wenzhou, Zhejiang, China 325027; yuanboliang@126.com.

ZL and TYG contributed equally to the work presented here and should therefore be regarded as equivalent authors.

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PURPOSE. To report the refractive error difference (RED) between parents and their children, and its risk factors, in a rural area of China.

METHODS. Children (6–17 years) and their parents (36.2 ± 4.1 years) from the Handan Offspring Myopia Study (HOMS) were enrolled. Cycloplegic autorefractometry (cyclopentolate 1%, Topcon KR8800) of the children and noncycloplegic autorefractometry of their parents were assessed. A detailed vision-based questionnaire was also completed. Refractive error difference was defined as the difference between the parental spherical equivalent (SE) and their children's SE. Generational myopic shift was defined as the estimated RED when a child would be 18 years old according to a prediction model.

RESULTS. Three hundred fifty-six pairs of parents and 585 children were enrolled. The RED (median, quartiles) increased from -1.33 (-1.99 , -0.98) diopters (D) in children aged 6 to 7 years to 0.81 (-0.16 , 2.28) D in children aged 16 to 17 years. The children's SE was predicted to approach the parental SE at 14 years of age. Moreover, the children's estimated myopic shift would be 1.03 D. Multiple linear regression revealed that older children ($\beta = 0.23$ D/y, $P < 0.0001$) and girls ($\beta = 0.24$, $P = 0.01$) tended to have a higher RED.

CONCLUSIONS. In this rural Chinese population, the children's refraction was estimated to be similar to the parental refraction at 14 years of age. Moreover, the generational myopic shift was estimated to be approximately 1 D at 18 years of age. These data suggest that the generational difference reflects the increasing prevalence of myopia in the younger generation, which is likely due to changes in environmental exposure.

Keywords: refractive error, myopia, risk factors

Myopia is the most common visual disorder affecting children in both the rural and urban populations in East Asia.^{1–6} Epidemiological studies have found a remarkable increase in the prevalence of myopia in children in this area.^{7–9} Lin et al.⁸ found that the prevalence of myopia in 12-year-old children increased from 36.7% in 1983 to 61.0% in 2000. In China, the prevalence of myopia in the Chinese adult (40 years or older) population in urban (Beijing) and rural (Handan) areas is similar (approximately 20%).^{10,11} However, the prevalence of myopia and the average refractive error in 15-year-old children in urban China (Guangzhou) are 78.4% and -1.50 diopters (D), respectively,² which is significantly greater than in children of the same age residing in rural China (e.g., Yangxi, a rural area located west of Guangzhou) (43.0% and -0.50 D, respectively).³ These data suggest that differences in lifestyle and exposure to environmental factors between parents and their

children, as well as between the rural and urban younger generation in China, may be important factors.^{12–16}

Our recent report from the Beijing Myopia Progression Study (BMPS) demonstrated that the predicted age when a child's spherical equivalent (SE) was similar to the average SE of his or her parents was 11 years, and furthermore that the generational myopic shift from parents to their children was 1.94 D in urban Beijing.¹⁶ Estimation of the myopic shift between these two generations appears to reflect environmental effects, such as more intensive near work, longer educational duration, and less outdoor activity,^{8,9} on the development of myopia in this relatively short span of time. There may also be a difference in the effect of environmental factors on the development of myopia between the urban and rural younger generation.^{3,13,17} Hence, given the relatively close genetic backgrounds among people living in the urban and rural areas in the same region, it is useful to compare the generational myopic shift between the two areas.

The Handan Offspring Myopia Study (HOMS) was designed to determine the prevalence of myopia among rural children, namely, the offspring of the Handan Eye Study (HES) population,¹⁸ especially with respect to family history.¹⁹ The HOMS also investigated the correlation between childhood and parental myopia.¹⁹ It is noteworthy that children from the HOMS were in the same age range as those in the BMPS and received vision examinations (e.g., visual acuity, ocular biometry, cycloplegic autorefraction) and questionnaires similar to those in the BMPS.^{19,20}

The aim of this study was to determine the age-specific refractive error difference (RED) between parents and their children and the risk factors for RED in the HOMS, and furthermore to compare the generational myopic shift between the rural and urban areas of China.

METHODS

Subjects

Details, rationale, design, and methodology of the HOMS were reported elsewhere.¹⁹ Briefly, in 2006 to 2007, a population-based eye study in adults (30 years and older), the Handan Eye Study (HES), in Handan, Hebei Province of Northern China, was conducted.¹⁸ In that study, 6830 Han people from 13 randomly selected villages in the Yongnian County of Handan were recruited.¹⁸ Six of the 13 villages where all people aged ≥ 30 years had participated in the HES were selected for the HOMS. A total of 1238 children from the six villages, along with at least one of their parents who participated in the HES, were eligible for the HOMS. Between March 2010 and June 2010, 878 of the 1238 (70.9%) children were recruited into the current study.¹⁹ All children received comprehensive vision examinations and a detailed vision-related questionnaire. For parents who did not participate in the HES, the vision examinations were performed during the HOMS.

Children who underwent cycloplegic refraction and both parents who underwent noncycloplegic refraction were included in the present study. The exclusion criteria were (1) children or parents with amblyopia or strabismus, (2) children or parents with a history of either intraocular surgery or penetrating ocular trauma, and (3) children or parents with severe medical or ocular health problems. The study followed the tenets of the Declaration of Helsinki and was approved by the ethics committee of the Handan Eye Hospital. Parental written informed consent and the children's assent were obtained from the children's parents/guardians and the children themselves.

Refractive Error

Cycloplegia was performed in all children using two drops of 1% cyclopentolate (Cyclogyl; Alcon, Fort Worth, TX, USA), administered 5 minutes apart, with a third drop administered after 20 minutes. Pupils were considered to be fully dilated if the diameter was larger than 6 mm, and cycloplegia was recorded as being present and complete if the pupillary light reflex was absent.¹⁹ Cycloplegic refraction of each eye was performed using an objective autorefractor-keratometer (KR8800; Topcon, Tokyo, Japan). The parental noncycloplegic refraction was performed using the same objective autorefractor in both HES and HOMS.

Questionnaire

The questionnaire used in the Sydney Myopia Study²¹ (available at <http://www.cvr.org.au/sms.htm>) was translated into Chinese with minor modifications.^{16,19} The purpose of

this questionnaire was to survey the child's near work, outdoor activity, books read per week, and living environment. The average hours spent on near work activity were totaled for drawing, homework, reading, and handheld computer use. Time spent on outdoor activities was evaluated on the basis of responses to queries regarding playing outdoors, family picnics and barbecues, bicycle riding, hiking, and outdoor sports. Activity levels were graded into population quartiles of the average daily hours spent on these different activities.²²

Definitions

The children's refractive error was defined as the combined average of the cycloplegic SE (sphere + 1/2 cylinder) of both eyes. The parental refractive error was assumed to have undergone no or minor change within 4 years, and it was defined as the combined average noncycloplegic SE of the father and mother (four eyes). Refractive error difference was defined as the mean difference between the refractive error of both eyes of the parents and their respective children, that is, mean parental SE minus children's SE.¹⁶ Myopia and high myopia were defined as SE < -0.50 D and SE < -5.0 D, respectively.^{11,19}

Data Analysis

The data analysis methods were consistent with our previous report on the generational myopic shift in urban China.¹⁶ The RED of each family was calculated and then averaged in each age group. Since the number of subjects in some age subgroups (i.e., children aged 15, 16, or 17 years) was less than 20, adjacent age groups were combined to reduce the variation of further estimation. Both the median RED and the proportion of children with myopic SE higher than that of their parents as a function of the children's combined age were calculated and presented. Since there were families with more than one child, generalized estimating equations (GEEs) were used to establish fitting functions to investigate the trend of the RED and proportion of children having a myopic SE higher than mean parental SE. The binominal fitted functions with the RED (D)/proportion (percentage) of higher myopic SE as the dependent variable, and the children's original age (years) as the independent variable, were fitted. These had the largest R^2 and smallest quasi-likelihood under the independence model criterion (QIC) as compared to other comprehensive fitting functions such as linear or logarithmic functions. The generational myopic shift was defined as the estimated RED predicted by the binominal fitted function at 18 years of age, since the age of myopic stabilization in the majority of children was reported to be less than 18 years.²³ Generalized estimating equations were also used to determine the association between RED and the putative risk factors assessed from the questionnaire after adjusting for the children's age and sex.

Data with either a normal or non-normal distribution were presented as the mean \pm 1 standard deviation and the median (quartiles), respectively. Statistical significance was determined using the rank-sum test (non-normal distribution). Statistical analysis was performed with Statistical Analysis System for Windows version 9.1.3 (SAS, Inc., Cary, NC, USA). A P value less than 0.05 was considered to be statistically significant.

RESULTS

A total of 369 families (369 pairs of parents and 613 children) with completed refractive error data were enrolled. Twenty-two pairs of parents and 28 children were excluded due to having amblyopia, strabismus, or intraocular surgical history of

TABLE 1. Characteristics of the Children and Their Parents

	Total
Sex, male:female	323:262
Age, y, mean \pm SD	
Children	10.6 \pm 2.5
Father	36.4 \pm 4.2
Mother	36.0 \pm 4.3
Refractive error, D, median (quartiles)	
Children*	0.28 (−0.40, 0.75)
Father*	−0.31 (−0.88, 0.00)
Mother*	−0.38 (−0.75, 0.00)
Parents†	−0.38 (−0.78, −0.06)
Myopia, <i>n</i> (%)‡	
Children	136 (23.3)
Fathers	212 (36.2)
Mothers	221 (37.8)
High myopia, <i>n</i> (%)‡	
Children	4 (0.68)
Fathers	9 (1.54)
Mothers	2 (0.34)
Myopic parents, number (%)‡	
None	231 (39.5)
Either	275 (47.0)
Both	79 (13.5)

* Refractive error was defined as the average spherical equivalent of both eyes.

† Refractive error was defined as the average spherical equivalent of father and mother.

‡ Myopia was defined as SE < −0.50 D; high myopia was defined as SE < −5.0 D.

SD, standard deviation.

a family member. Three hundred fifty-six families (356 pairs of parents and 585 children), including 323 boys (55.2%) and 262 girls (44.8%), were enrolled and used in the final analysis. There were 176, 134, 43, and 3 families with one, two, three, and four children, respectively. The mean (\pm SD) age of the children was 10.6 \pm 2.5 years (range, 6–17 years). The mean (\pm SD) age of the fathers and mothers was 36.4 \pm 4.2 years and 36.0 \pm 4.3 years, respectively. The SE [median, (quartiles)] of the children and parents was 0.28 (−0.40, 0.75) D and −0.38 (−0.78, −0.06) D, respectively (Table 1). There were 136 (23.3%), 212 (36.2%), and 221 (37.8%) myopic children, myopic fathers, and myopic mothers, respectively. There were 231 (39.5%), 275 (47.0%), and 79 (13.5%) children with no, one, or two myopic parents, respectively (Table 1).

Children aged 6 to 13 years had a more hyperopic SE as compared to their parents ($P < 0.05$). There was no significant difference in the SE of the parents and children aged 14 to 15 years ($P = 0.31$), while in children aged 16 to 17 years, a more myopic SE was found in the children as compared to their parents ($P = 0.026$) (Table 2). The RED [median, (quartiles)] was −1.33 (−1.99, −0.98) D in the 6- to 7-year-old children. Only 1.6% (1/64) of the children aged 6 to 7 years exhibited a higher myopic SE than their parents. At the age of 14 to 15 years, the RED was 0.03 (−0.84, 1.18) D and hence close to zero; that is, the children's SE approximated the average SE of their parents. Of the children aged 14 to 15 years, 52.9% (27/51) exhibited a higher myopic SE than their parents. However, by age 16 to 17 years, the RED increased to 0.81 (−0.16, 2.28) D, and 68.4% (13/19) of the children had a higher myopic SE than their parents.

Table 3 shows the associations between RED and the putative risk factors. In the univariate linear analysis, children who were older, and girls who spent more time on near work activity, tended to have higher RED. However, after adjusting for the children's age and/or sex, only children who were older ($\beta = 0.23$ D/year, $P < 0.0001$) and girls ($\beta = 0.24$, $P = 0.01$) tended to have a significantly higher RED. No significant differences were found among the different levels of parental education, near work, outdoor activity, books read per week, and living environments (Table 3). In urban areas, children who were older ($\beta = 0.46$ D/year, $P < 0.0001$), spent less time on outdoor activity ($\beta = -0.21$ D/hours per day, $P = 0.02$), had less paternal education ($\beta = -0.26$, $P = 0.027$), and had less maternal education ($\beta = -0.27$, $P = 0.033$) tended to have a significantly higher RED, after adjusting for the children's age and sex (for variable age, only sex was adjusted).

Table 4 presents the estimated RED and the proportion of children having a higher myopic SE than the mean parental SE in both the rural and urban areas. The Figure presents the urban and rural binomial fitting curves of RED. Using the binomial fitted function, the rural children's predicted SE would be similar to their parents' at the age of 14 years, which is 3 years later than in the urban children. Furthermore, the estimated generational myopic shift in the rural children would be 1.03 D (95% confidence interval, 0.74–1.62 D) at the age of 18 years, which is approximately 1 D less than that found in urban children. Slightly less than half (48.9%) of the children would have a higher myopic SE than their parents at the age of 14 years, and the estimated proportion would reach 84.2% at the age of 18 years.

DISCUSSION

There were several interesting and important findings in the current study. First, the proportion of children having a higher

TABLE 2. Number and Refractive Error of the Children and Their Parents in the Different Age Groups

Children's Age, y	Number	Refractive Error, D*, Median (Quartiles)		
		Children	Parents	<i>P</i> Value†
6–7	64	0.84 (0.51, 1.25)	−0.50 (−0.81, −0.24)	<0.001
8–9	140	0.59 (0.12, 0.97)	−0.38 (−0.78, −0.12)	<0.001
10–11	178	0.15 (−0.31, 0.59)	−0.39 (−0.78, −0.03)	<0.001
12–13	133	0.06 (−0.94, 0.43)	−0.34 (−0.78, −0.06)	0.013
14–15	51	−0.47 (−1.43, 0.41)	−0.34 (−0.78, 0.03)	0.31
16–17	19	−0.65 (−2.56, 0.22)	−0.09 (−0.50, 0.16)	0.026

* Children's refractive error was defined as the average spherical equivalent of both eyes; parental refractive error was defined as the average spherical equivalent of father and mother.

† *P* value using rank-sum test.

TABLE 3. Age- and Sex-Adjusted Refractive Error Difference Between Parents and Their Children and Its Association With Risk Factors Using Generalized Estimating Equations

	<i>N</i>	Mean \pm SD	Crude		Adjusted	
			β	<i>P</i>	β	<i>P</i>
Sex*						
Male	323	−0.71 \pm 1.31	0.00	Ref	0.00	Ref
Female	262	−0.31 \pm 1.41	0.40	<0.001	0.24	0.01
Father's education†						
Primary and less	184	−0.52 \pm 1.20	0.00	Ref	0.00	Ref
Junior middle school	345	−0.54 \pm 1.39	−0.03	0.84	−0.12	0.29
Senior middle school and above	42	−0.54 \pm 1.80	−0.03	0.91	−0.10	0.69
Trend test			−0.02	0.85	−0.08	0.41
Near work activity						
1st quartile, lowest	162	−0.78 \pm 1.18	0.00	Ref	0.00	Ref
2nd quartile	138	−0.45 \pm 1.55	0.33	0.04	0.10	0.49
3rd quartile	149	−0.42 \pm 1.17	0.36	0.02	−0.03	0.83
4th quartile	135	−0.45 \pm 1.55	0.34	0.03	0.03	0.84
Trend test			0.11	0.03	−0.002	0.97
Outdoor activity						
1st quartile, lowest	159	−0.60 \pm 1.39	0.00	Ref	0.00	Ref
2nd quartile	139	−0.59 \pm 1.26	0.02	0.92	−0.15	0.23
3rd quartile	143	−0.33 \pm 1.46	0.27	0.09	0.09	0.53
4th quartile	143	−0.61 \pm 1.35	−0.01	0.96	−0.21	0.16
Trend test			0.02	0.63	−0.04	0.39
Books read per week, number						
≤2	560	−0.55 \pm 1.36	0.00	Ref	0.00	Ref
>2	24	−0.24 \pm 1.68	0.31	0.29	0.12	0.73
Continuous reading, min‡						
0–15	109	−0.61 \pm 1.39	0.00	Ref	0.00	Ref
16–30	237	−0.58 \pm 1.19	0.03	0.84	0.04	0.81
31–45	173	−0.56 \pm 1.46	0.05	0.79	−0.11	0.47
>45	65	−0.16 \pm 1.66	0.45	0.04	0.17	0.48
Trend test			0.11	0.08	0.007	0.92
Placing face unusually close to the book while reading/writing						
No	533	−0.56 \pm 1.33	0.00	Ref	0.00	Ref
Yes	30	−0.32 \pm 1.96	0.24	0.35	0.41	0.14
High buildings in front of the house						
No	503	−0.58 \pm 1.37	0.00	Ref	0.00	Ref
Yes	65	−0.25 \pm 1.45	0.33	0.07	0.11	0.50
The horizon in front of the house						
No	385	−0.59 \pm 1.35	0.00	Ref	0.00	Ref
Yes	160	−0.39 \pm 1.46	0.20	0.13	0.06	0.64

* Only age was adjusted.

† No mother's education data are presented, since results were similar.

‡ Continuous reading was defined as time spent continuously reading before taking a rest period of 5 minutes or longer.

SD, standard deviation; Ref, reference group.

myopic SE than their parents increased as the children's age increased, similar to findings in an urban area.¹⁶ Second, with an estimation model similar to that used in an urban study,¹⁶ at the age of 14 years, the SE of the rural children was predicted to be similar to that of their parents. Furthermore, the estimated rural generational myopic shift would be 1.03 D. In our previous urban study, the predicted similarity in SE between the children and their parents would be attained at the age of 11 years, and the estimated generational myopic shift would be 1.94 D.¹⁶ Hence, there was approximately a 3-year delay between the urban and rural children with respect to attainment of the mean parental refractive error. More

importantly, the generational myopic shift was approximately 1 D less in the rural versus the urban children (Fig.).¹⁶ Since there was greater underestimation of the generational myopic shift in the hospital-based urban study¹⁶ due to the presence of a greater myopic parental refractive error, the difference in generational myopic shift between the rural and urban area would be predicted to be even greater than 1 D. Third, it was found that older children and girls tended to have a high RED in the rural area (Table 3).

People in the same part of the country (Northern China) share extremely close genetic backgrounds, including that for myopia. Hence, the children would be predicted to inherit and

TABLE 4. Age-Specified Estimated Refractive Error Difference Between Parents and Their Children, and the Estimated Proportion of Children with a Myopic Spherical Equivalent Higher Than Mean Parental SE, in Rural and Urban Areas

Children's Age, y	RED		Higher Myopic Proportion	
	Rural Area	Urban Areas	Rural Area	Urban Areas
6	−1.45	−2.86	1.4	0.0
7	−1.29	−2.18	5.6	3.0
8	−1.12	−1.56	10.4	17.6
9	−0.95	−0.98	15.6	30.7
10	−0.76	−0.45	21.3	42.3
11	−0.57	0.02	27.5	52.2
12	−0.37	0.45	34.1	60.6
13	−0.16	0.82	41.3	67.5
14	0.06	1.15	48.9	72.7
15	0.29	1.42	57.0	76.5
16	0.53	1.64	65.6	78.6
17	0.77	1.82	74.6	79.2
18	1.03	1.94	84.2	78.2

Data on urban areas are reported with permission from Liang et al., 2013.¹⁶

develop a refractive error similar to that of their parents if no other factors were involved. However, a different urban–rural RED was found (Fig.). This difference may be due to the presence of a greater myopic refractive error in both the parents and children in the urban as compared to the rural area.¹⁶

Several factors may have contributed to the different urban–rural RED. First, Guo et al.²⁴ recently reported that urban region of habitation was associated with the presence of myopia and longer ocular axial length in grade 1 primary students in Beijing. Urban children are putatively exposed to more intensive near work and less outdoor activity as compared to rural children from an early age.^{24,25} It is also expected that the impact of near work or any other environmental risk factor for myopia would be cumulative over time.²⁶ Hence, over several years, urban children might exhibit a higher RED as compared to their parents, such that they would attain the average parental refraction approximately 3 years earlier. Second, it should be noted that migration from a rural to an urban area was very common in the last generation, while the rural population was much more stable. Thus, some of the children living in an urban area may be exposed to more myopigenic environmental factors than their rural-origin parents. Hence, differences in environmental factors such as time spent in myopigenic activities, as well as the educational pressure difference between the two genera-

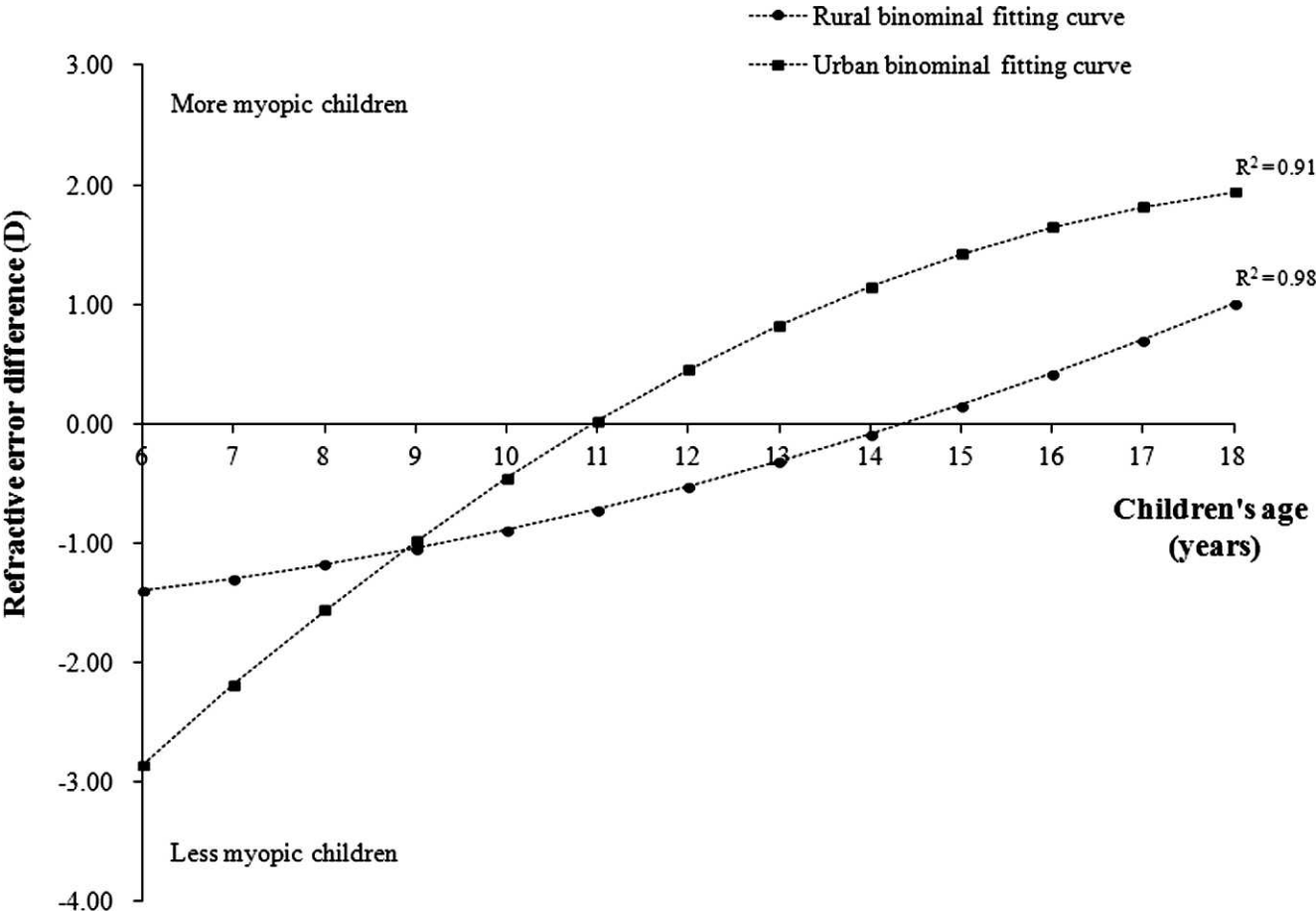


FIGURE. Binominal fitting curve for refractive error difference (RED) from parents to children in the rural area of China (black circles, $n = 585$) as a function of children's age, and the binominal fitting curve in an urban area of China from Liang et al. (black rectangles). The rural binominal fitting functions for rural children and urban children were $RED = 0.0044a^2 + 0.10a - 2.21$ and $RED = -0.025a^2 + 1.01a - 8.00$, respectively ($a =$ children's age). RED was defined as parental spherical equivalent minus their children's spherical equivalent. The figure was reproduced with permission from Liang YB, Lin Z, Vasudevan B, et al. Generational difference of refractive error in the baseline study of the Beijing Myopia Progression Study. *Br J Ophthalmol*. 2013;97:765–769.

tions at similar age/school levels (e.g., more educational pressure in primary school for children than for their parents), would be important factors in predicting the RED. This may also explain the different magnitudes of generational myopic shift between urban and rural areas.

Epidemiological studies have found a remarkable increase in the prevalence of myopia in a given area in both children⁷⁻⁹ and adults.^{9,27,28} In our previous urban study¹⁶ and in the current one in a rural area, an increase in myopic refraction from the parents to their children was found, as well as different magnitudes of generational myopic shift between the urban and rural areas. Furthermore, the final, stable myopic level would be expected to be consistent over two generations if only a physiologically based progression were presumed to exist. In the urban area, children who spent less time on outdoor activity were associated with higher RED after adjusting for their age and sex. Hence, we believe the cohort effect (i.e., increase in exposure to environmental factors) plays an important role in the myopic shift between the two generations over the last three decades. However, in the rural area, the RED was not found to be associated with environmental factors such as near work, outdoor activity, books read per week, near reading distance, or a close living environment after adjusting for the same confounders. It is noteworthy that in the rural area, the near work load was relatively low (Table 3), as most children read fewer than two books per week (95.9%), did not read continuously for more than 45 minutes (88.9%), and did not write with materials close to their eyes (95.2%). In addition, outdoor activity time in the rural children (approximately 3 hours per day) was relatively longer than in the urban children (less than 2 hours per day).²⁹ Spacious living environments, which may be associated with less myopia,³⁰ were common in the rural area, as very few houses were close to high buildings (11.4%). Based on these factors, we believe that the negative associations between RED and the risk factors in our cross-sectional study may be due to relatively less exposure and shorter accumulated duration for these risk factors. Further long-term explorations are required to investigate the effect of such environmental factors.

There are some possible limitations to the present study. First, there may have been an underestimation of the generational myopic shift for reasons similar to those in our urban study.¹⁶ The mean noncycloplegic SE of 16- to 45-year-old subjects was estimated to be approximately 0.4 D more myopic than their cycloplegic SE.³¹ In addition, the myopia may continue to progress after the age of 18 years in some subjects.^{32,33} Second, there was undersampling in some age groups. Third, only children aged 6 to 17 years were enrolled in this study. It would be optimal to include young adults older than 18 years of age as well. This would help to predict the generational myopic shift more accurately. Further studies with larger sample sizes and wider age ranges are warranted. Last, the refractive error information for the nonresponding children (approximately 30%) was unknown.

In summary, the present study found that rural children's SE was predicted to be similar to the average SE of their parents at the age of 14 years. More importantly, the estimated generational myopic shift would be approximately 1 D in rural China. Less generational myopic shift in rural Chinese children was found as compared to urban Chinese children. This generational difference in refraction was consistent with the increasing prevalence of myopia in the younger generation, which is likely due to changes in environmental exposure.

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